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Docket No. 25401-26

PATENT

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Holly D Kozlowski

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Ib Mendel-Hartvig et al	:	Paper No.:
Serial No.:	09/582,808	:	Group Art Unit: 1641
Filed:	October 16, 2000	:	Examiner: G. Counts

For: **Analytical Method Using Particles and Test Kit for Performing the Method**

TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Submitted herewith in **triplicate** is a revised Appeal Brief in support of the Notice of Appeal filed June 24, 2004 and received June 28, 2004 and in response to the Notification of Non-Compliant Appeal Brief dated November 21, 2005. Please charge any additional fees required or credit any excess in fees paid in connection with the present communication to Deposit Account No. 04-1133.

Respectfully submitted,

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For: **Analytical Method Using Particles and Test Kit for Performing the Method**

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by Certificate of Mail on June 24, 2004 and received by the U.S. Patent and Trademark Office on June 28, 2004 and in response to the Notification of Non-Compliant Appeal Brief dated November 21, 2005.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of the present application, Pharmacia Diagnostics AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' undersigned legal representative or the assignee which will directly effect or be directly effected by or having a bearing on the Board's decision in the present appeal. However, the Board may consider the copending appeal in Application Serial No. 09/582,734 to be of interest. Appellants' original Appeal Brief also referred to the copending appeal in Application Serial No. 09/582,741; however, Application Serial No. 09/582,741 has now issued as U.S. Patent No. 6,916,666 B1.

III. STATUS OF THE CLAIMS

Claims 42-83 are pending in this application and stand rejected. Claims 1-41 are cancelled. A copy of the claims on appeal is set forth in the Appendix.

IV. STATUS OF AMENDMENT FILED SUBSEQUENT TO REJECTION ON APPEAL

An Amendment Under 37 C.F.R. §1.116 was filed by certificate of mailing on June 24, 2004. The Supplementary Advisory Action dated August 26, 2004 indicated that the Amendment would be entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention is directed to methods and test kits using biospecific affinity reactions in combination with an analytically detectable reactant, referred to as Reactant*, to determine an analyte in a sample (specification, page 1, lines 1-8).

More particularly, as defined by claim 42, the present invention is directed to a method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction (specification, page 1, lines 5-15). The method comprises allowing an analytically

detectable reactant (Reactant*) and the sample comprising the analyte to migrate through channels in a flow matrix to a detection zone located in the matrix, in which there is a firmly anchored biospecific affinity reactant (Capturer), and capturing the Reactant* in the detection zone in an amount related to the amount of analyte in the sample (specification, page 1, lines 5-15). According to claim 63, the invention is directed to a test kit for performing analytical methods in a flow matrix utilizing biospecific affinity reactions to detect an analyte in a sample (specification, page 1, lines 5-15). The kit comprises (i) a flow matrix having a detection zone in which there is firmly anchored biospecific affinity reactant (Capturer), and (ii) an analytically detectable reactant (Reactant*) (specification, page 3, lines 6-10).

In both the method of claim 42 and the test kit of claim 63, the Reactant* has labeled particles as an analytically detectable group, and the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface (specification, page 3, lines 6-16). The particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone (specification, page 3, lines 12-26).

According to claims 43 and 64, immobilization of a biospecific affinity reactant by covalent binding is to the hydrophilic groups on the Capturer particles (specification, page 5, lines 8-11). According to claims 44 and 65, a mixture of biospecific affinity reactants is immobilized to the hydrophilic groups on the Capturer particles (specification, page 6, line 37-page 7, line 12). According to claims 45 and 66, a mixture of biospecific affinity reactants found in allergen extracts is immobilized to the hydrophilic groups on the Capturer particles (specification, page 6, line 37-page 7, line 3). According to claims 46 and 67, a mixture of biospecific affinity reactants found in biological material used to detect autoantibodies is immobilized to the hydrophilic groups on the Capturer particles (specification, page 6, line 37-page 7, line 12).

Claims 47 and 68 specify that the hydrophilic groups are hydroxy, carboxy, amino or sulphonate groups (specification, page 12, lines 15-17).

Claims 48 and 69 specify that the analyte is an antibody of IgE or IgG type with specificity to allergens, while claims 49 and 70 specify that the analyte is an antibody of IgG, IgM or IgA type with specificity to autoantigens (specification, page 14, lines 13-17).

According to claims 50 and 71, the particles anchoring the Capturer have a size in the range of 0.1-100 μm and the flow channels of the matrix have a smallest inner dimension in the range of 0.4-100 μm (specification, page 3, lines 24-28; page 8, lines 2-6). According to claims 51 and 72, and claims 52 and 73, the particles which anchor the Capturer have a size in the range of 0.1-1000 μm, and in the range of 0.1-100 μm, respectively (specification, page 3, lines 24-28).

According to claims 53 and 74, the labeled particles in the Reactant* have a diameter in the range of 0.01-5 μm (specification, page 5, lines 14-17).

According to claims 54 and 75, and claims 55 and 76, the flow channels have a smallest inner diameter in the range of 0.4-1000 μm, and in the range of 0.4-100 μm, respectively (specification, page 8, lines 2-6).

Claims 56 and 77 recite that the labeled particles are fluorescent or coloured (specification, page 5, lines 29-33).

Claims 57 and 78 recite that the Reactant* is predeposited in the matrix upstream of the DZ, while claims 58 and 79 recite that the Reactant* is predeposited in the matrix upstream of a sample application site (specification, page 11, lines 23-25; page 13, lines 14-16).

Claims 59 and 80 recite that the particles which anchor the Capturer to the matrix are a synthetic polymer, a semisynthetic polymer or a biopolymer, which on its surface exhibits hydrophilic groups (specification, page 3, lines 12-16 and line 33-page 7, line 9).

According to claims 60 and 81, the Reactant* is captured in the DZ by formation of a ternary complex of Reactant'-analyte-Reactant*, wherein the Reactant* binds to the analyte simultaneously or in sequence and Reactant' is the firmly anchored Capturer or a reactant to which the Capturer binds by biospecific affinity (specification, page 10, line 4-page 11, line 23). Claims 61 and 82 specify that the analyte is an antigen and the Reactant' and Reactant* are antibodies with specificity for epitopes on the analyte (specification, page 14, lines 7-33).

Finally, claims 62 and 83 recite that the method is performed in connection with diagnosing allergy or autoimmune disease (specification, page 15, lines 7-8).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are on appeal for review by the Board:

A. The rejection of claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 under 35 U.S.C. §103(a) as being unpatentable over the Charlton et al U.S. Patent No. 5,989,921 in view of the Batz et al U.S. Patent No. 4,415,700 and the Brown et al U.S. Patent No. 5,149,622.

B. The rejection of claims 44-46 and 65-67 under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Bennich et al U.S. Patent No. 3,720,760.

C. The rejection of claims 48, 50, 54, 55, 69, 71, 75 and 76 under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Devlin et al U.S. Patent No. 5,846,703.

D. The rejection of claims 49, 58, 70 and 79 under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Dafforn et al U.S. Patent No. 4,981,786.

E. The rejection of claims 62 and 83 under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Self U.S. Patent No. 4,446,231.

VII. ARGUMENTS

As will be set forth in detail below, Appellants submit that the methods and test kits according to the present invention are nonobvious over and patentably distinguishable from the cited combinations of Charlton et al, Batz et al and Brown et al, even in further view of Bennich et al, Devlin et al, Dafforn et al or Self. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed. Favorable action by the Board is respectfully requested.

A. Charlton et al, Batz et al and Brown et al

The methods and test kits defined by claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al and Brown et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

Appellants submit that claims 47 and 68 are independently patentable from claims 42 and 63 from which they depend; Appellants concede that claims 43, 51-53, 56, 59, 59-61, 64, 72-74, 77 and 80-82 stand or fall together with claims 42 or 63, from which they respectively depend. Reasons in support of the independent patentability of the respective claims are set forth below.

1. The Examiner's Position

In rejecting claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al in view of Batz et al and Brown et al, the Examiner asserted that Charlton et al disclose an immunoassay method and device with a test site comprising latex particles entrapped or fixed

in the flow path and having an immobilized protein (antibody/capturer) on their surface. The Examiner admitted that Charlton et al fail to teach immobilized particles which exhibit hydrophilic groups on their surfaces or that the particles have a size which is smaller than the smallest inner dimension of the flow channels of the matrix. The Examiner asserted that Batz et al disclose hydrophilic particles as a carrier for biologically and/or immunologically active substances covalently bound to the particles for use in immunoassays. The Examiner asserted that Brown et al disclose a fluid device in which particles having a substance capable of reaction with an analyte in a sample are immobilized in a matrix, wherein a particle of a size smaller than the flow channels of the matrix is used to provide an improved solid-phase analytical device.

2. The Claimed Invention

As defined by claim 42, the present invention is directed to a method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction. The method comprises allowing an analytically detectable reactant (Reactant*) and the sample comprising the analyte to migrate through channels in a flow matrix to a detection zone located in the matrix, in which there is a firmly anchored biospecific affinity reactant (Capturer), and capturing the Reactant* in the detection zone in an amount related to the amount of analyte in the sample. According to claim 63, the invention is directed to a test kit for performing analytical methods in a flow matrix utilizing biospecific affinity reactions to detect an analyte in a sample. The kit comprises (i) a flow matrix having a detection zone in which there is firmly anchored biospecific affinity reactant (Capturer), and (ii) an analytically detectable reactant (Reactant*).

In both the claimed methods and test kits, the Reactant* has labeled particles as an analytically detectable group, and the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface. The particles anchoring the

Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. Thus, the Capturer is predisposed in the flow channels of the flow matrix by the immobilized particles exhibiting hydrophilic groups on their surface. As set forth in the present specification, including the examples, such methods and test kits wherein the Reactant* has labeled particles as an analytically detectable group and the Capturer is anchored within the flow channels of the matrix by immobilized particles which exhibit hydrophilic groups on their surface, provide surprisingly improved analytical detection of an analyte in a sample.
In this regard, attention is directed to the specification, for example at page 4, line 15 - page 5, line 12 wherein the marked hydrophobic character of polystyrene particles is discussed. While the hydrophobicity of polystyrene causes it to be adsorbed very strongly to nitrocellulose flow membranes, the hydrophobic features of the particles have been found to promote non-specific adsorption of labeled reactant (Reactant*) and/or analyte, thereby decreasing the sensitivity of test methodologies. On the other hand, the methods and test kit according to the invention, wherein the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface, promote covalent bonding of biospecific affinity reactants to the particles and as such decreases the tendency of non-specific adsorption of labeled reactant and/or analyte in a detection zone.

3. The Claims are Nonobvious over the Cited Combination

Charlton et al disclose a test cell and a method for detection of a preselected ligand in a liquid sample. Charlton et al disclose that the method involves the step of transporting the sample and a conjugate comprising a protein bound to a metal sol or other colored particle along a flow path and in contact with a test site comprising immobilized binding protein specific to an epitope of the ligand. Charlton et al broadly disclose that the test site comprises latex particles trapped or otherwise fixed in the flow path having the immobilized protein on

their surface (column 3, lines 25-37), and specifically disclose the use of latex beads comprising polystyrene particles passively coated with purified rapid anti-human chorionic gonadotropin (column 7, lines 61-64).

However, Appellants find no teaching or suggestion by Charlton et al relating to a method or test kit as defined in claims 42 and 63 wherein a biospecific affinity reactant (Capturer) is firmly anchored to a flow matrix via immobilized particles exhibiting hydrophilic groups on their surface, particularly in combination with an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group. As discussed above, the present specification notes, for example, beginning at page 4, line 21, that while a hydrophobic particle such as the polystyrene employed by Charlton et al is absorbed very strongly to flow matrices such as nitrocellulose membranes, the hydrophobic features of the particles promote non-specific absorption of analytically detectable reactant (Reactant*) and/or analyte and therefore decrease the specificity and accuracy of assays. In the present invention, the immobilized particles which anchor the Capturer to the matrix exhibit hydrophilic groups on their surface. As the specification notes, for example beginning at page 5, line 8, introduction of the hydrophilic groups on the particles facilitates covalent binding of biospecific affinity reactants to the particles and decreases the tendency of non-specific absorption in the detection zone. Appellants find no teaching or suggestion by Charlton et al relating to immobilized particles exhibiting hydrophilic groups on their surface, or any advantage provided thereby.

The deficiencies of Charlton et al are not resolved by Batz et al and Brown et al. For example, Batz et al disclose hydrophilic latex particles consisting of a homo- or a co-polymer of monomers which are sparingly soluble in water and a process for the preparation of such particles. Batz et al further disclose the use of such particles as carrier materials for biological and/or immunologically active substances in diagnostic agents. Particularly, as

demonstrated in Examples 10-13 at columns 8-12 of Batz et al, the particles are used for solution immunoassays (see, for example, column 9, lines 50-60; column 10, line 58 - column 11, line 6; and column 11, lines 17-49). Appellants find no teaching or suggestion by Batz et al relating to a flow matrix immunoassay or use of the latex particles described therein in a flow matrix immunoassay. In fact, Appellants find no teaching or suggestion by Batz et al that their latex particles are suitable for adsorption to a second solid support or matrix. Moreover, Appellants find no teaching, suggestion or recognition by Batz et al that their particles will provide improved sensitivity in flow matrices and decrease the tendency of non-specific absorption in a detection zone of a flow matrix as is obtained according to the present invention.

The Examiner has asserted that it is within the realm of ordinary skill in the art to replace one solid phase particle (that of Batz et al) for another solid phase particle (that of Charlton et al) because the use of such particles is well known in the art. However, obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Clearly, that two references relate to the same general technology is not sufficient, as the prior art which the Federal Circuit found deficient in *Geiger* all related to water treatment technology. Nevertheless, the Court found that the requisite teaching, suggestion or incentive supporting the combination of prior art was absent. Similarly, in the present rejection, that Charlton et al and Batz et al each disclose particles for use in assay techniques is not sufficient absent some teaching, suggestion or incentive supporting the combination. To the contrary, in view of the disclosures of Charlton et al and Batz et al, at best, one skilled in the art might find it obvious to try various combinations of their

disclosures. However, as noted by the Court in *Geiger*, this is not the standard for patentability.

The Examiner appears to rely on the disclosure of Batz et al indicating that their hydrophilic particles provide a diagnostic agent which has covalently bound biological and/or immunological active substances which do not impair the structure and thus the activity of the biologically active proteins. However, in view of Batz et al's concern for impairment of reactant activity (see, for example, column 2, line 63-column 3, line 2), one of ordinary skill in the art would be disinclined to absorb such particles to a second solid support, as one of ordinary skill in the art would presume that such adsorption would impair the structure and thus the activity of the biologically active proteins with which Batz et al are concerned. Thus, the concerns which Batz et al attempt to overcome would lead one of ordinary skill in the art away from the combination asserted by the Examiner. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). Thus, Batz et al do not resolve the deficiencies of Charlton et al.

In the Advisory Action, the Examiner asserted that the concern regarding impairment of reactant activity is an assertion not supported by the evidence. It appears that the Examiner has misunderstood the Appellants' position. That is, Batz et al clearly indicate a concern regarding impairment of reactant activity, see, for example, column 2, line 63-column 3, line 2. The plain teachings of Batz et al therefore would not motivate one of ordinary skill in the art to employ particles of Batz et al in another solid support, or to expect any improvement from such a combination. Thus, the evidence of record teaches one of ordinary skill in the art away from the combination of references asserted by the Examiner.

Brown et al disclose a solid-phase analytical device for use in solid-phase binding assays to determine the presence or amount of an analyte in a test sample. In the paragraph

bridging columns 8 and 9, Brown et al disclose the use of substantially spherical solid particles retained and immobilized upon fibers of a porous fiber matrix material. Brown et al specifically disclose that

> "the size of the particles is not critical, and so long as the average diameter of the particles is substantially within the aforestated range (although it is preferred that the average diameter of the particles be smaller than the average pore size of the fibrous matrix), any type of particles having the foregoing properties is suitable for use" (column 9, lines 11-17).

The referenced range is from about 0.1 to about 10 microns or more, most preferably from about 0.1 to about 5 microns (column 8, lines 53-56). However, Appellants find no teaching by Brown et al that the particle size is smaller than the flow channels of the matrix or, as required by the present claims, that the *particles have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix*, as is required by claims 42 and 63. To the contrary, Brown et al merely refer to *average* diameters. Thus, Brown et al neither teach nor suggest the limitations required by the present claims.

As Brown et al fail to teach or suggest the limitation of the present claims that the particles have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix, the combination asserted by the Examiner of Charlton et al and Brown et al does not result in a flow matrix to which capturer is anchored as required by the present claims. The Examiner has asserted that Brown et al teach the average diameter of the particles is less than the average pore size of the matrix, again failing to appreciate the difference between this teaching in Brown and the limitations required by claims 42 and 63. The Examiner has further asserted that the optimum dimension in diameter of the flow channels and particle size can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. However, it is not obvious to optimize a parameter not recognized as a result-effective variable, *In re Antonie*, 195 U.S.P.Q 6 (CCPA 1977), and Brown et al

provide no teaching or suggestion as to any import of particle size. To the contrary, Brown et al disclose that the size of the particles is "not critical" (column 9, lines 11-17).

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). As noted, Batz et al fail to teach or suggest the use of their latex particles in a flow matrix or in combination with any other type of solid support, and Brown et al fail to teach a method and flow matrix as presently claimed, wherein particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. In view of these deficiencies, Batz et al and Brown et al in combination with Charlton et al do not enable one of ordinary skill in the art to make and use the presently claimed methods and test kits.

Thus, the methods and test kits defined by claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 are nonobvious over and patentably distinguishably from the combination of Charlton et al, Batz et al and Brown et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

4. Claims 47 and 68 are Independently Patentable

Claims 47 and 68 specify that the hydrophilic groups are hydroxy, carboxy, amino or sulphonate groups. On the other hand, Batz et al disclose that their hydrophilic character is provided by epoxide groups (column 3, lines 30-32). Appellants find no teaching or suggestion by Charlton et al, Batz et al and Brown et al of a method or test kit as recited in claims 47 and 68 and requiring, inter alia, Capturer anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface, wherein the hydrophilic groups are hydroxy, carboxy, amino or sulphonate groups.

In view of these deficiencies, Batz et al and Brown et al in combination with Charlton et al do not enable one of ordinary skill in the art to make and use the methods and test kits of claims 47 and 58, and therefore do not render the claimed invention obvious, *Motorola, Inc. v. Interdigital Tech. Corp., supra* .

Thus, the methods and test kits defined by claims 47 and 58 are nonobvious over and patentably distinguishably from the combination of Charlton et al, Batz et al and Brown et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

B. Charlton et al, Batz et al, Brown et al and Bennich et al

The methods and test kits defined by claims 44-46 and 65-67 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al, Brown et al and Bennich et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

Appellants concede that claims 44-46 and 65-67 stand or fall together.

1. The Examiner's Position

Claims 44-46 and 65-67 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of Bennich et al. The Examiner relied on Bennich et al as disclosing test allergens immobilized to particles and disclosing that the test allergen can be a mixture of two or more allergens. The Examiner asserted it would have been obvious to incorporate test allergens taught by Bennich et al into the modified method of Charlton et al.

2. The Claimed Invention

According to claims 44 and 65, a mixture of biospecific affinity reactants is immobilized to the hydrophilic groups on the Capturer particles. According to claims 45 and 66, a mixture of biospecific affinity reactants found in allergen extracts is immobilized to the hydrophilic groups on the Capturer particles. According to claims 46 and 67, a mixture of

biospecific affinity reactants found in biological material used to detect autoantibodies is immobilized to the hydrophilic groups on the Capturer particles.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Charlton et al in view of Batz et al and Brown et al with respect to claims 42 and 63, from which claims 44-46 and 65-67 depend, are discussed in detail above and apply equally well to the subject matter of claims 44-46 and 65-67. Moreover, the deficiencies of these references with respect to the subject matter of claims 44-46 and 65-67 are not resolved by Bennich et al.

That is, Bennich et al disclose an in vitro method for determining the presence of reagin-Ig in a sample wherein a test allergen comprising one single allergen or a mixture of two or more allergens may be employed (column 4, lines 56-57). However, Bennich et al, like Batz et al, relate to a method wherein particles are contacted with a sample in a solution, and Appellants find no teaching or suggestion by Bennich et al relating to the use of a flow matrix as required by the present claims. Accordingly, the teachings of Bennich et al do not resolve the basic deficiencies of the combination of Charlton et al, Batz et al and Brown et al. That Bennich et al teach the use of a combination of allergens in a process in which particles are contacted with a sample in a solution is not relevant to the patentability of the presently claimed methods and test kits which employ a flow matrix and are directed to the objective of improving the specificity and accuracy of methods and test kits employing a flow matrix. It is therefore submitted that the rejection of claims 44-46 and 65-67 under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Bennich et al should be reversed.

C. Charlton et al, Batz et al, Brown et al and Devlin et al

The methods and test kits defined by claims 48, 50, 54, 55, 69, 71, 75 and 76 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz

et al, Brown et al and Devlin et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

Appellants submit that claims 48 and 69 are independently patentable and that claims 50, 54, 55, 71, 75 and 76 are independently patentable, while conceding that claims 50, 54, 55, 71, 75 and 76 stand or fall as a group. Reasons in support of the independent patentability of the respective claims are set forth below.

1. The Examiner's Position

Claims 48, 50, 54, 55, 69, 71, 75 and 76 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of Devlin et al. The Examiner asserted it would have been obvious to incorporate the use of immobilized antigens as taught by Devlin et al into the modified method of Charlton et al.

2. The Claimed Invention

Claims 48 and 69 specify that the analyte is an antibody of IgE or IgG type with specificity to allergens.

According to claims 50 and 71, the particles anchoring the Capturer have a size in the range of 0.1-100 μm and the flow channels of the matrix have a smallest inner dimension in the range of 0.4-100 μm. According to claims 54 and 75, and claims 55 and 76, the flow channels have a smallest inner diameter in the range of 0.4-1000 μm, and in the range of 0.4-100 μm, respectively.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Charlton et al in view of Batz et al and Brown et al with respect to claims 42 and 63, from which claims 48, 50, 54, 55, 69, 71, 75 and 76 depend, are discussed in detail above and apply equally well to the subject matter of claims 48, 50, 54, 55, 69, 71, 75 and 76. Moreover, the deficiencies of these references with respect to the subject matter of claims 48, 50, 54, 55, 69, 71, 75 and 76 are not resolved by Devlin et al.

For example, Devlin et al disclose fluorescence immunoassays using fluorescent dyes free of aggregation and serum binding. Devlin et al broadly disclose that the sandwich techniques disclosed therein can be used to assay antibodies rather than antigens wherein the antigen coupled to a solid phase is used as a first receptor. Beginning at column 4, line 56, Devlin et al briefly discuss the use of enzyme-enhanced fluorescence technology which combines microparticle capture and antigen-antibody reaction with an enzyme rate reaction using a fluorescent enzyme substrate.

However, Appellants find no teaching or suggestion by Devlin et al relating to a method or test kit as presently claimed, or for modifying the teachings of Charlton et al to provide such a method or test kit. Particularly, Appellants find no teaching or suggestion by Devlin et al for a method or test kit employing a flow matrix as presently claimed wherein an analytically detectable reactant (Reactant*) has labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) is anchored to the flow matrix via immobilized particles of a size and function as claimed and exhibiting hydrophilic groups on their surface. Similarly, Appellants find no teaching or suggestion by Devlin for modifying the teachings of Charlton et al to provide such a combination, or relating to any benefit provided by either a flow matrix method or test kit employing such a combination.

Further, with respect to claims 48 and 69, Appellants find no teaching or suggestion by Devlin et al relating to a method or test kit employing a flow matrix for detection of IgE or IgG type with specificity to allergens. Rather, the teachings at columns 2 and 3 generally referencing IgE relate to solution techniques. Thus, once again, the Examiner applies the teachings of prior art which are not relevant to flow matrix methods and devices.

With respect to claims 50, 54, 55, 71, 75 and 76, Appellants find no teaching or suggestion by Devlin et al which would lead one of ordinary skill in the art to select the range

sizes as recited in these claims, particularly since Appellants find no teaching or suggestion by Devlin et al of a flow matrix method or device.

Thus, the cited combination of Charlton et al, Batz et al, Brown et al and Devlin et al does not enable one skilled in the art to conduct the claimed methods or to make and use the claimed test kits. Thus, these references do not in combination render the presently claimed methods and test kits obvious, *Motorola, Inc. v. Interdigital Tech. Corp., supra.* The rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Devlin et al should therefore be reversed.

D. Charlton et al, Batz et al, Brown et al and Dafforn et al

The methods and test kits defined by claims 49, 58, 70 and 79 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al, Brown et al and Dafforn et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

Appellants submit that claims 49 and 70 are independently patentable and that claims 58 and 79 are independently patentable. Reasons in support of the independent patentability of the respective claims are set forth below.

1. The Examiner's Position

Claims 49, 58, 70 and 79 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of Dafforn et al. The Examiner asserted it would have been obvious to incorporate the application of reagents and the detection of autoimmune antibodies as taught by Dafforn et al into the modified method of Charlton et al.

2. The Claimed Invention

Claims 49 and 70 specify that the analyte is an antibody of IgG, IgM or IgA type with specificity to autoantigens. Claims 58 and 79 recite that the Reactant* is predeposited in the matrix upstream of a sample application site.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Charlton et al in view of Batz et al and Brown et al with respect to claims 42 and 63, from which claims 49, 58, 70 and 79 depend, are discussed in detail above and apply equally well to the subject matter of claims 49, 58, 70 and 79. Moreover, the deficiencies of these references with respect to the subject matter of claims 49, 58, 70 and 79 are not resolved by Dafforn et al.

That is, Dafforn et al disclose a multiple port assay device for capturing a first member of a specific binding pair in a zone and for allowing liquid to be transported by capillary action away from the zone. Delivery of a sample may be made into the device through a first means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample may be added to the device through a second means. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42).

However, Appellants find no teaching or suggestion by Dafforn et al relating to a method or test kit as presently claimed employing, in combination, an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a Capturer which is anchored to the matrix by immobilized particles as defined and exhibiting hydrophilic groups on their surface. Similarly, Appellants find no teaching or suggestion by Dafforn et al relating to any improvement provided by a method or a test kit employing such a Reactant* and immobilized Capturer in combination. Further, Appellants find no teaching

or suggestion for modifying the teachings of Charlton et al to incorporate any or all of the teachings of Dafforn et al, and particularly Appellants find no teaching or suggestion in either reference for modifying the teachings of Charlton et al along the lines of the presently claimed methods and test kits.

With respect to claims 49 and 70, Appellants find no teaching by Dafforn et al relating to a method which specifically determines an analyte which is an antibody of IgG, IgM or IgA type with specificity to autoantigens. Broad reference by Dafforn et al to autoimmune antibodies does not suggest either the method or device of these claims.

Additionally, Appellants find no teaching by Dafforn et al of the limitations of claims 58 and 79, that the Reactant* is predeposited in the matrix upstream of a sample application site. Column 13, lines 32-44 referenced by the Examiner merely disclose application of a liquid reagent, but provide no teaching or suggestion of Reactant* predeposited in the matrix upstream of a sample application site.

In view of these deficiencies in the teachings of Dafforn et al, the combination of Dafforn et al with Charlton et al, Batz et al and Brown et al does not enable one of ordinary skill in the art to perform the presently claimed methods or to make and use the claimed test kits. Thus, the combination of Charlton et al, Batz et al, Brown et al and Dafforn et al does not render the presently claimed methods and test kits obvious under 35 U.S.C. §103, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*. The rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Dafforn et al should therefore be reversed.

E. <u>Charlton et al, Batz et al, Brown et al and Self</u>

The methods and test kits defined by claims 62 and 83 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al, Brown et al and Self, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

Applicants concede that claims 62 and 83 stand or fall together.

1. The Examiner's Position

Claims 62 and 83 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of Self. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

2. The Claimed Invention

Claims 62 and 83 recite that the method is performed in connection with diagnosing allergy or autoimmune disease.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Charlton et al in view of Batz et al and Brown et al with respect to claims 42 and 63, from which claims 62 and 83 depend, are discussed in detail above and apply equally well to the subject matter of claims 62 and 83. Moreover, the deficiencies of these references with respect to the subject matter of claims 62 and 83 are not resolved by Self.

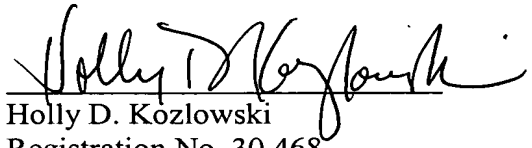
Self discloses an immunoassay using an amplified cyclic detection system. At column 1, beginning at line 39, Self broadly discloses that immunoassays may be used for qualitative or quantitative determinations and that color reactions and precipitation reactions, for example, using latex particles for visualization, may be used. However, Appellants find no teaching or suggestion by Self relating to methods or test kits as presently claimed employing a combination of an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) anchored to a flow matrix via immobilized particles as claimed which exhibit hydrophilic groups on their surface. Similarly, Appellants find no teaching or suggestion by self for modifying the teachings of Charlton to provide such methods or test kits, or relating to any advantage provided thereby. Thus, the combination of Charlton et al, Batz et al, Brown et al

and Self does not enable one of ordinary skill in the art to conduct the presently claimed methods or to make and use the presently claimed test kits. Accordingly, the combination of Charlton et al, Batz et al, Brown et al and Self does not render the presently claimed methods and test kits obvious. Thus, the rejection of claims 62 and 83 under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Self should be reversed.

VIII. CONCLUSIONS

Thus, the methods and test kits defined by claims 42-83 are nonobvious over and patentably distinguishable from the cited combinations of Charlton et al, Batz et al and Brown et al, even in further view of Bennich et al, Devlin et al, Dafforn et al or Self. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed. Favorable action by the Board is respectfully requested.

Respectfully submitted,



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APPENDIX

Claim 42. A method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction, which method comprises:

i. allowing an analytically detectable reactant (Reactant*) and a sample comprising the analyte to migrate through flow channels in a flow matrix to a detection zone (DZ) located in the matrix, in which there is a firmly anchored biospecific affinity reactant (Capturer), and

ii. capturing the Reactant* in the DZ in an amount related to the amount of analyte in the sample,

wherein

A) the Reactant* has labeled particles as an analytically detectable group, and

B) the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface, wherein the particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone.

Claim 43. The method according to claim 42, wherein immobilization of a biospecific affinity reactant by covalent binding is to the hydrophilic groups on the Capturer particles.

Claim 44. The method according to claim 42, wherein a mixture of biospecific affinity reactants is immobilized to the hydrophilic groups on the Capturer particles.

Claim 45. The method according to claim 42, wherein a mixture of biospecific affinity reactants found in allergen extracts is immobilized to the hydrophilic groups on the Capturer particles.

Claim 46. The method according to claim 42, wherein a mixture of biospecific affinity reactants found in biological material used to detect autoantibodies is immobilized to the hydrophilic groups on the Capturer particles.

Claim 47. The method according to claim 42, wherein the hydrophilic groups are hydroxy, carboxy, amino or sulphonate groups.

Claim 48. The method according to claim 42, wherein the analyte is an antibody of IgE or IgG type with specificity to allergens.

Claim 49. The method according to claim 42, wherein the analyte is an antibody of IgG, IgM or IgA type with specificity to autoantigens.

Claim 50. The method according to claim 42, wherein the particles anchoring the Capturer have a size in the range of 0.1-100 μm and the flow channels of the matrix have a smallest inner dimension in the range of 0.4-100 μm.

Claim 51. The method according to claim 42, wherein the particles which anchor the Capturer have a size in the range of 0.1-1000 μm.

Claim 52. The method according to claim 42, wherein the particles which anchor the Capturer have a size in the range of 0.1-100 μm.

Claim 53. The method according to claim 42, wherein the labeled particles in the Reactant* have a diameter in the range of 0.01-5 μm.

Claim 54. The method according to claim 42, wherein the flow channels have a smallest inner diameter in the range of 0.4-1000 μm.

Claim 55. The method according to claim 42, wherein the flow channels have a smallest inner dimension in the range of 0.4-100 μm.

Claim 56. The method according to claim 42, wherein the labeled particles are fluorescent or coloured.

Claim 57. The method according to claim 42, wherein the Reactant* is predeposited in the matrix upstream of the DZ.

Claim 58. The method according to claim 57, wherein the Reactant* is predeposited in the matrix upstream of a sample application site.

Claim 59. The method according to claim 42, wherein the particles which anchor the Capturer to the matrix are a synthetic polymer, a semisynthetic polymer or a biopolymer, which on its surface exhibits hydrophilic groups.

Claim 60. The method according to claim 42, wherein the Reactant* is captured in the DZ by formation of a ternary complex of Reactant'-analyte-Reactant*, wherein the Reactant* binds to the analyte simultaneously or in sequence and Reactant' is the firmly anchored Capturer or a reactant to which the Capturer binds by biospecific affinity.

Claim 61. The method according to claim 60, wherein the analyte is an antigen and the Reactant' and Reactant* are antibodies with specificity for epitopes on the analyte.

Claim 62. The method according to claim 42, wherein the method is performed in connection with diagnosing allergy or autoimmune disease.

Claim 63 (Currently Amended): A test kit ~~when used~~ for performing analytical methods in a flow matrix, which methods utilize biospecific affinity reactions to detect an analyte in a sample, which kit comprises (i) a flow matrix having a detection zone (DZ), in which there is a firmly anchored biospecific affinity reactant (Capturer), and (ii) and analytically detectable reactant (Reactant*),

wherein

A) the Reactant* has labeled particles as an analytically detectable group, and

B) the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface, wherein the particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels and do not interfere with detection of Reactant* in the detection zone.

Claim 64. The kit according to claim 63, wherein immobilization of a biospecific affinity reactant by covalent binding is to the hydrophilic groups on the Capturer particles.

Claim 65. The kit according to claim 63, wherein immobilization of a complex mixture of biospecific affinity reactants is to the hydrophilic groups on the Capturer particles.

Claim 66. The kit according to claim 63, wherein immobilization of a complex mixture of biospecific affinity reactants found in allergen extracts is to the hydrophilic groups on the Capturer particles.

Claim 67. The kit according to claim 63, wherein immobilization of a complex mixture of biospecific affinity reactants found in biological material used to detect autoantibodies is to the hydrophilic groups on the Capturer particles.

Claim 68. The kit according to claim 63, wherein the hydrophilic groups are hydroxy, carboxy, amino or sulphonate groups.

Claim 69. The kit according to claim 63, wherein the analyte is an antibody of IgE or IgG type with specificity to allergens.

Claim 70. The kit according to claim 63, wherein the analyte is an antibody of IgG, IgM or IgA type with specificity to autoantigens.

Claim 71. The kit according to claim 63, wherein the particles anchoring the Capturer have a size in the range of 0.1-100 μm and the flow channels of the matrix have a smallest inner dimension in the range of 0.4-100 μm.

Claim 72. The kit according to claim 63, wherein the particles which anchor the Capturer have a size in the range of 0.1-1000 μm.

Claim 73. The kit according to claim 63, wherein the particles which anchor the Capturer have a size in the range of 0.1-100 μm.

Claim 74. The kit according to claim 63, wherein the labeled particles in the Reactant* have a diameter in the range of 0.01-5 μm.

Claim 75. The kit according to claim 63, wherein the flow channels have a smallest inner dimension in the range of 0.4-1000 μm.

Claim 76. The kit according to claim 63, wherein the flow channels have a smallest inner dimension in the range of 0.4-100 μm.

Claim 77. The kit according to claim 63, wherein the labeled particles are fluorescent or coloured.

Claim 78. The kit according to claim 63, wherein the Reactant* is predeposited in the matrix upstream of the DZ.

Claim 79. The kit according to claim 78, wherein the Reactant* is predeposited in the matrix upstream of a sample application site.

Claim 80. The kit according to claim 63, wherein the particles which anchor the Capturer to the matrix are a synthetic polymer, a semisynthetic polymer or a biopolymer, which on its surface exhibits hydrophilic groups.

Claim 81. The kit according to claim 63, wherein the Reactant* is captured in the DZ by formation of a ternary complex of Reactant'-analyte-Reactant*, wherein the Reactant* binds to the analyte simultaneously or in sequence and Reactant' is the firmly anchored Capturer or a reactant to which the Capturer is capable of binding by biospecific affinity.

Claim 82. The kit according to claim 81, wherein the analyte is an antigen and the Reactant' and Reactant* are antibodies with a specificity for epitopes on the analyte.

Claim 83. The kit according to claim 63, wherein the method is performed in connection with diagnosing allergy or autoimmune disease.

EVIDENCE APPENDIX

There is no evidence relied upon in the present Appeal Brief.

RELATED PROCEEDINGS APPENDIX

There are no proceedings related to the present appeal.

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